Obesity and renal cancer incidence and mortality – a systematic review of prospective cohort studies

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Abstract
Introduction and objective. There have been many studies published recently on obesity and the risk of renal cancer; however, the epidemiological evidence for such an association has not been consistent. Therefore, a systematic review was conducted of the prospective cohort studies to assess the association between obesity and the risk of renal cancer incidence and death.

Materials and methods. A search was conducted of the PubMed database and references to published studies from inception until May 2013. Guidelines for Assessing Quality in Prognostic Studies on the Basis of Framework for Potential Biases were followed for quality assessment of studies included in the systematic review.

Results. Twenty eligible studies were identified and included in the systematic review. Among the 20 selected studies, overall study quality was high. Although the evidence from the prospective cohort studies, linking obesity with renal cancer incidence, has not been entirely consistent, there is a convincing body of data for a positive relationship. Moreover, cumulative data is compelling for a strong positive association between obesity and fatal renal cancer.

Conclusions. There is a relatively consistent amount of evidence that obesity increases the risk of renal cancer and fatal renal cancer. Further research is needed as better understanding of mechanisms by which obesity may influence renal cancer development and progression will aid the fostering of strategies for prevention and treatment of one of the most lethal human malignancies.

Key words. obesity, renal cancer, incidence, mortality, systematic review

INTRODUCTION

Being overweight and obese have become major public health challenges worldwide [1, 2, 3]. It has recently been estimated that overweight (body mass index (BMI) ≥25 kg/m²) affects more than one billion people, and more than 300 million of them are considered obese (BMI ≥30 kg/m²) [4]. The trend has been continuing to escalate over the last 20 years, both in the United States and Europe, where the prevalence of obesity among adults has doubled [5, 6].

Being overweight and obese are recognised risk factors for many chronic medical conditions and several types of cancer, including colorectal, endometrial and prostate [7, 8, 9, 10, 11, 12]. Their potential link to renal cancer, which represents 2–3% of all cancers in the developed countries, with 88,400 new cases of renal cell carcinoma and 39,300 kidney cancer-related deaths in the European Union in 2008, has attracted the attention of many clinicians [13, 14, 15, 16, 17]. As a result, a large number of studies have been published recently, with three-quarters of the world’s publications written over last decade.

The evidence for an association between obesity and renal cancer incidence and mortality, however, has not been consistent. This may result, in part, from the nature of epidemiologic studies, particularly case-controlled or retrospective, which are more prone to a number of biases. In the absence of randomised trials of weight-change interventions, large well-constructed prospective cohort analyses would instead provide the highest level of evidence.

Therefore, to address the issues described above, a systematic review was carried out of the prospective cohort studies on body weight and the risk of renal cancer incidence and mortality.

OBJECTIVE

This review sought to answer the question: ‘What evidence is there for an association between obesity and renal cancer incidence and mortality?’

MATERIALS AND METHOD

A systematic review of prospective cohort studies was undertaken in order to accurately identify, evaluate and
summarise the findings of all relevant studies. To ensure the complete and transparent reporting of this systematic review, the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) checklist was used as a tool to guide the structure of the review [18].

**Search strategy.** A comprehensive search strategy was used on the Medline/PubMed electronic database from its inception until May 2013. Additionally, the search was complemented by scanning the reference lists of the identified studies and the reference lists of previous systematic reviews [19, 20, 21].

All human research articles published in English were taken into consideration, not classified as review, meta-analysis, editorial, comment, letter, guideline, or news. The search strategy included the following terms: obesity, overweight, BMI, nutrition disorder, diet, nutrition assessment, risk, incidence, mortality, kidney cancer, renal cancer, renal cell cancer, renal carcinoma and renal cell carcinoma.

To be included in the review, studies had to fulfill the following criteria:
1) have a prospective design;
2) be a cohort study;
3) exposure of interest was weight or BMI at baseline and/or at the end of follow-up;
4) the outcome of interest was a renal cancer and/or fatal renal cancer;
5) hazard ratio (HRs) estimates with 95% confidence intervals (CIs) or, alternatively, continuous relative risk (RR) estimates (with 95% CIs), or alternatively, RR estimates (with 95% CIs).

**Data extraction.** The following data was extracted from each study: last name of the first author, publication year, country where the study was conducted, cohort size, duration of follow-up, how BMI or body weight was assessed, age at baseline, per cent of overweight and obese subjects, number of renal cancer and fatal renal cancer cases, HRs or RR estimates with corresponding 95% CIs and p values.

**Quality assessment.** Guidelines for Assessing Quality in Prognostic Studies on the Basis of Framework for Potential Biases were followed for quality assessment of studies included in the systematic review [22]. The potential risk for bias was evaluated within the 6 following domains: (i) study participation; (ii) study attrition; (iii) prognostic factors measured; (iv) outcome measurement; confounding measurement and account; (v) analysis.

Two authors performed quality assessment independently. There was no disagreement between the two assessments.

**RESULTS**

**Study selection.** A flow chart of the selection of eligible studies is given in Figure 1. Eligibility assessment was performed independently by 2 reviewers, in duplicate. The search strategy yielded 15,185

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**Figure 1. Flow diagram of studies identified**

Records identified through electronic database searching = 1,5175

Additional records identified through manual searches of the bibliographies of selected publications=10

218 studies for analysis of title and abstracts after duplicates removed

170 studies excluded based on title and/or abstract

48 full-text articles assessed for eligibility

28 full-text articles excluded:
Not a prospective cohort study=19
Overlapping studies=5
Relation of weight with cancer not provided=4

20 studies included in qualitative synthesis
citations, of which 218 were considered potentially relevant. 170 of these were excluded after screening titles and abstracts. The full text of the remaining 48 studies was assessed; of those, 19 were rejected, as the study was not a prospective cohort, and 4 studies did not report on the relation of weight and/or BMI with renal cancer and/or fatal renal cancer. To avoid duplicate information from overlapping studies, 5 studies were removed because their results were pooled or updated. The remaining 20 studies were included in the presented review [23–42]. A chronological overview of the eligible studies is provided in Table 1.

Table 1. Characteristics and results of prospective cohort studies of the association between anthropometric measures and renal cancer incidence and mortality

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Study location</th>
<th>Cohort size and gender</th>
<th>Follow-up</th>
<th>BMI Measured or Self-reported</th>
<th>Age range</th>
<th>Percent overweight and obese at baseline</th>
<th>No of cases</th>
<th>Reported HRs(a) or RR (b) for renal incidence</th>
<th>Reported HRs (a) or RR (b) for renal cancer death</th>
<th>Reported (95%CI) and p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leiba</td>
<td>2013</td>
<td>Israel</td>
<td>1,110,835 (M)</td>
<td>15.9</td>
<td>Measured</td>
<td>16-19</td>
<td>12.1% BMI&gt;25</td>
<td>274(II)</td>
<td>a BMI=25.0-27.4 1.16 for BMI=25.0-27.4 2.43 for BMI≥27.5</td>
<td>(0.72-1.87)</td>
<td>p=0.54 (1.54-3.83) p&lt;0.001</td>
</tr>
<tr>
<td>Joh</td>
<td>2011</td>
<td>USA</td>
<td>118,177 (W)</td>
<td>32</td>
<td>Self-reported</td>
<td>30-55</td>
<td>?</td>
<td>330(II)</td>
<td>a 1.00 for BMI&lt;30 1.22 for BMI≥30</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Sawada</td>
<td>2010</td>
<td>Japan</td>
<td>99462 (M+W)</td>
<td>13.5</td>
<td>Self-reported</td>
<td>40-69</td>
<td>27.4% BMI≥25</td>
<td>139(II)</td>
<td>Men: a 1.39 for BMI=25-26.9 1.99 for BMI=27 Women: a 1.55 for BMI≥25</td>
<td>(0.73-2.63)</td>
<td>(1.04-3.81) p=0.76-3.18</td>
</tr>
<tr>
<td>Adams</td>
<td>2008</td>
<td>USA</td>
<td>320,618 (M+W)</td>
<td>8.2</td>
<td>Self-reported</td>
<td>50-71</td>
<td>?</td>
<td>1022(II)</td>
<td>b BMI=25-27.5 1.49 for BMI=25-27.5 1.67 for BMI=27.5-30 1.97 for BMI=30-35 2.56 for BMI≥35</td>
<td>(1.19-1.88)</td>
<td>(1.32-2.12) (1.56-2.50)</td>
</tr>
<tr>
<td>Song</td>
<td>2008</td>
<td>Korea</td>
<td>152,772 (W)</td>
<td>8.75</td>
<td>Measured</td>
<td>40-64</td>
<td>?</td>
<td>111(II)</td>
<td>a BMI=23.0-24.9 1.74 for BMI=25.0-26.9 1.37 for BMI=27.0-29.9 2.61 for BMI≥30</td>
<td>(0.94-3.22)</td>
<td>(0.92-3.29) (0.66-2.84)</td>
</tr>
<tr>
<td>Reeves</td>
<td>2007</td>
<td>UK</td>
<td>1,222,630 (W)</td>
<td>5.4 (I)</td>
<td>Self-reported</td>
<td>50-64</td>
<td>35.6% (ov) 17.9% (ob)</td>
<td>723(II)</td>
<td>a BMI=25-27.5 1.10 for BMI=25-27.5 1.19 for BMI=27.5-30 1.52 for BMI≥30</td>
<td>(0.94-1.28)</td>
<td>(0.99-1.44) (1.31-1.77) p=0.005</td>
</tr>
<tr>
<td>Luo</td>
<td>2007</td>
<td>USA</td>
<td>140,057 (W)</td>
<td>7.7</td>
<td>Measured</td>
<td>50-79</td>
<td>?</td>
<td>269(II)</td>
<td>b BMI=25-29.9 1.2 for BMI=29.9 1.5 for BMI=30.0-34.9 1.6 for BMI≥35</td>
<td>(0.9-1.7)</td>
<td>(1.0-2.1) (1.1-2.4) p=0.01</td>
</tr>
<tr>
<td>Setiawan</td>
<td>2007</td>
<td>Hawaii</td>
<td>75,162 (M) 85,964 (W)</td>
<td>8.3</td>
<td>Self-reported</td>
<td>45-75</td>
<td>Men: a 42.5% (ov) 13.8% (ob) Women: 30.1% (ov) 18.0% (ob)</td>
<td>220(I)</td>
<td>b Men: a 1.14 (ov) 1.76 (ob) Women: 2.03 (ov) 2.27 (ob)</td>
<td>(0.84-1.55)</td>
<td>(1.20-2.58) p=0.005 (1.31-3.15) (1.37-3.47) p=0.001</td>
</tr>
<tr>
<td>Samanic</td>
<td>2006</td>
<td>Sweden</td>
<td>362,552 (M)</td>
<td>19</td>
<td>Measured</td>
<td>?</td>
<td>?</td>
<td>734(II)</td>
<td>b 1.28 (ov) 1.82 (ob)</td>
<td>(1.10-1.49)</td>
<td>(1.41-2.35)</td>
</tr>
</tbody>
</table>
Table 1. Characteristics and results of prospective cohort studies of the association between anthropometric measures and renal cancer incidence and mortality (Continuation)

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Study location</th>
<th>Cohort size and gender</th>
<th>Follow-up</th>
<th>BMI Measured or Self-reported</th>
<th>Age range</th>
<th>Percent overweight and obese at baseline</th>
<th>No of cases</th>
<th>Reported HRs(a) or RR (b) for renal incidence</th>
<th>Reported (95%CI) and p value</th>
<th>Reported HRs (a) or RR (b) for renal cancer death</th>
<th>Reported (95%CI) and p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pischon</td>
<td>2006</td>
<td>European countries</td>
<td>348,550 (M+W)</td>
<td>6.0</td>
<td>Measured and for part self-reported</td>
<td>25-70</td>
<td>25.1% BMI≥26.0</td>
<td>155(I) (M) 132(I) (W)</td>
<td>Men: b 0.67 for BMI=25.4-27.0 0.84 for BMI=27.1-29.3 1.22 for BMI≥29.4</td>
<td>(0.39-1.18) (0.49-1.43) (0.74-2.03)</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Lukanova</td>
<td>2006</td>
<td>Sweden</td>
<td>33,424 (M) 35,362 (W)</td>
<td>8.2</td>
<td>Measured</td>
<td>29-61</td>
<td>Men: 46% (ov) 11% (ob) Women: 31% (ov) 13% (ob)</td>
<td>25(I) (M) 20(I) (W)</td>
<td>Men: b 1.30 (ov) 3.63 (ob) Women: 0.92 (ov) 1.79 (ob)</td>
<td>(0.51-3.56) (1.23-10.66)</td>
<td>p=0.02</td>
<td>(0.31-2.58) (0.55-5.27)</td>
</tr>
<tr>
<td>Flaherty*</td>
<td>2005</td>
<td>USA</td>
<td>48,953 (M)</td>
<td>12</td>
<td>Self-reported</td>
<td>40-75</td>
<td>52.5% (ov) 7.8% (ob)</td>
<td>110(I)</td>
<td>Men: b 1.30 (ov) 3.63 (ob) Women: 0.92 (ov) 1.79 (ob)</td>
<td>(0.9-6.8)</td>
<td>(0.7-6.6)</td>
<td>p=0.019</td>
</tr>
<tr>
<td>Oh</td>
<td>2005</td>
<td>Korea</td>
<td>781,283 (M)</td>
<td>10</td>
<td>Measured</td>
<td>≥20</td>
<td>?</td>
<td>562(I)</td>
<td>Men: b BMI=25.0-27.9 2.1 for BMI=28.0-29.9 2.1 for BMI=30</td>
<td>(1.02-1.67)</td>
<td>(1.37-2.52)</td>
<td>(0.59-3.46)</td>
</tr>
<tr>
<td>Bjørge</td>
<td>2004</td>
<td>Norway</td>
<td>2,001,230 (M+W)</td>
<td>23</td>
<td>Measured</td>
<td>14-74</td>
<td>?</td>
<td>382(I) (M) 2632(I) (W)</td>
<td>Men: b 1.18 (ov) 1.55 (ob) Women: 1.32 (ov) 1.85 (ob)</td>
<td>(1.11-1.26)</td>
<td>(1.36-1.76)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Van Dijk</td>
<td>2004</td>
<td>Netherlands</td>
<td>120,852 (M+W)</td>
<td>9.3</td>
<td>Self-reported</td>
<td>55-69</td>
<td>?</td>
<td>275(I)</td>
<td>Men: b BMI=25.0-26.9 1.46 for BMI=27.0-29.9 1.42 for BMI=30</td>
<td>(0.61-1.38)</td>
<td>(0.97-2.21)</td>
<td>(0.54-1.99)</td>
</tr>
<tr>
<td>Nikodemus</td>
<td>2004</td>
<td>USA</td>
<td>34,637 (W)</td>
<td>15</td>
<td>Self-reported</td>
<td>55-69</td>
<td>?</td>
<td>124(I)</td>
<td>Men: b BMI=25.0-27.4 1.87 for BMI=27.4-30.6 2.49 for BMI=30.6</td>
<td>(0.77-2.74)</td>
<td>(1.02-3.41)</td>
<td>(1.39-4.44)</td>
</tr>
<tr>
<td>Calle</td>
<td>2003</td>
<td>USA</td>
<td>900,053 (M+W)</td>
<td>16</td>
<td>Self-reported</td>
<td>≥30</td>
<td>?</td>
<td>7(I) 837(D) (M) 473(D) (W)</td>
<td>Men: b 1.18 for BMI=25.0-29.9 1.36 for BMI=30-34.9 1.70 for BMI=35-39.9 1.65 for BMI=30-34.9 1.70 for BMI=35-39.9 4.75 for BMI≥40.0</td>
<td>91.02-1.37</td>
<td>(1.06-1.74)</td>
<td>(0.99-2.92)</td>
</tr>
</tbody>
</table>
Study characteristics. The selected 20 prospective cohort studies on renal cancer were published between 1978 – 2013 and involved a total of 8,716,689 subjects. In 15 studies, the source of population was the general population [25, 26, 27, 28, 29, 30, 32, 33, 35, 36, 37, 38, 39, 40, 42]; one population was a cohort of university students [41]; one was military recruits [23] and 3 were professional groups [24, 31, 34]. Three studies analysed a potential relationship between weight and renal cancer in men only [23, 31, 35], while 5 limited their investigation solely to women [24, 27, 28, 29, 38]. Almost all populations were more than 90% Caucasian; 3 studies included only Asians [25, 27, 35] and 2 multiethnic populations [23, 30].

In one out of the 20 studies only weight and no BMI analysis was performed [41]. Anthropometric variables were measured in 9 studies [23, 27, 29, 31, 33, 35, 36, 40, 41]; in 10 studies they were self-reported [24, 25, 26, 28, 30, 34, 36, 37, 38, 39, 42]; and in one they were measured or self-reported [32]. A relationship between body weight and the risk of renal cancer and fatal renal cancer was analysed in one study [28]. In 17 studies, only incidence of renal cancer in relation to body weight was evaluated [23, 24, 25, 26, 27, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 40, 41] and 2 studies examined solely the association between body weight and the risk of fatal renal cancer [39, 42]. The ascertainment of incidental renal cancer was made through linkage to cancer registries in 11 studies [23, 26, 28, 30, 31, 33, 35, 36, 37, 38, 40]. One study relied on self-reported diagnosis [41]. In 4 studies, self-reported diagnosis was verified by linkage with the cancer register or medical records [24, 26, 29, 34]. A mixed system of linkage to cancer and pathology registers, health insurance records and self-reported diagnosis, depending on the study centre considered, was used in one study [32]. The ascertainment of fatal renal cancer cases was made through linkage to death register in 1 study [28]. One study relied on personal enquiries successively verified by linkage with death registers [42], and personal enquiries or death registers, depending on the length of follow-up period considered, were used in one study [39].

Study synthesis and analysis. Among the 20 selected studies, the overall study quality was high. Assessment of the risk of bias across the studies is presented in Table 2.

A marked positive relationship between anthropometric variables and renal cancer risk in men was reported in 9 studies [23, 25, 26, 30, 31, 33, 35, 36, 41], whereas in women...
The presented study has several methodological strengths, namely:
1) the focused review question;
2) a comprehensive and systematic literature search;
3) the collaboration of a multidisciplinary team of urologists, endocrinologists and health researchers, who used explicit and reproducible eligibility criteria and duplicate reproducible eligibility decisions and data extractions;
4) inclusion of prospective cohort studies only.

This systematic review did not provide a quantitative evaluation of data. Moreover, epidemiological data, even if obtained from prospective cohort studies, may not be completely deprived of selection and surveillance bias. Particularly, studies that failed to use cancer and/or death registries to obtain relevant data, would be more prone to these types of systematic error.

**DISCUSSION**

This systematic review presents epidemiological evidence on the potential role of abnormal body weight in the etiology of renal cancer. In order to provide more conclusive data, and reduce the risk of selection and information bias, the presented assessment was restricted to prospective cohort studies only, and excluded case-control studies. In all, there were 20 studies included in this review. The overall study quality was high. In one study, the cohort size was greater than 2,000,000 subjects, in 2 > 1,000,000 individuals and in 3 > 700,000. Their follow-up period varied from 5.4 – 23 years.

The abundance of data gathered in this systematic review supports the hypothesis that obesity may increase the risk of both renal cancer and fatal renal cancer, suggesting an important role for obesity in the initiation and progression of this neoplasm. The pathology underlying the association between obesity and increased risk of renal cancer, however, remains unclear. To-date, several mechanisms have been proposed, one of which suggests the involvement of insulin and insulin-like growth factor-1 (IGF-1), known to have potent cancer-promoting effects [43]. Moreover, oestrogens, as well as polymorphism and genotypic changes of the oestrogen receptor alpha gene, may also play a role [44].

In addition, lipid peroxidation, which is elevated in obese people, has been proposed to be involved in renal cancer development in experimental models; lipid peroxidation of the proximal renal tubules has also been demonstrated to be a necessary mechanistic pathway in chemically-induced renal carcinogenesis [45]. Byproducts of lipid peroxidation have been shown to react with renal DNA to form adducts, which subsequently can damage DNA [46]. This, in turn, may lead to mutations in proto-oncogenes and/or tumor suppressor genes, and result in changing a normal cell into one with a malignant phenotype [47].

Adipose tissue not only stores energy, but also functions as an endocrine organ [48]. Adiponectin, leptin and resistin are adipocyte-secreted peptide hormones that may influence renal cancer development through their demonstrated effects on inflammation, insulin resistance, cell growth and proliferation [49].

**STRENGTHS AND LIMITATIONS OF THE REVIEW.** The presented study has several methodological strengths, namely:

1) **the focused review question:**
2) **a comprehensive and systematic literature search:**
3) **the collaboration of a multidisciplinary team of urologists, endocrinologists and health researchers, who used explicit and reproducible eligibility criteria and duplicate reproducible eligibility decisions and data extractions:**
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**CONCLUSIONS**

In conclusion, there is a relatively consistent amount of evidence that obesity increases the risk of renal cancer and fatal renal cancer. Further research is needed for better understanding of the mechanisms by which obesity may influence renal cancer development and progression, and will be an aid to the fostering of strategies for the prevention and treatment of one of the most lethal human malignancies.
REFERENCES


